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RUBELLA AND RUBELLIFORM RASH[1]

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INTRODUCTION

The observations of Gregg and others that certain fetal anomalies may be correlated with a maternal history of rubella in the first trimester of pregnancy have greatly increased the importance of this disease (5, 11, 27). Clinical recognition of rubella has been complicated, however, by the wide range of other conditions which may also be accompanied by maculopapular rash. In this discussion, the clinical and epidemiological features of rubella will be described and the differential diagnosis of this disease reviewed. Emphasis will be placed on the role of newer viral agents in the production of rubella-like disease.

RUBELLA

The disease is widespread, occurring both sporadically and in epidemics. In temperate zones, it is most prevalent in the spring (11). The agent is probably acquired through droplets entering the upper respiratory tract but can also enter by way of the conjunctiva (11).

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Incubation periods following intranasal instillation of infected materials have varied from 12 to 20 days, and following intramuscular inoculation, from 12 to 16 days (2, 14). Observations on the naturally acquired disease indicate a range of 14 to 25 days, with a mode of about 18 days. Seemingly shorter incubation periods have occasionally been noted among close associates and family contacts. It is probable in such cases that infection was acquired from the contact before his disease became apparent. The demonstration that virus may be present in nasopharyngeal secretions and occasionally in feces, as early as 6 to 7 days prior to rash, provides support for this hypothesis (8, 16).

In children, the prodrome is generally short and mild and may even be absent. Occasionally, especially in adults, it is more severe, persisting for 4 or 5 days, with fever, headache, malaise, and mild respiratory symptoms.

Adenopathy, preceding the rash by as long as 7 days and involving especially the posterior auricular, cervical, and suboccipital groups, is a prominent feature of the disease (8, 15). It is generally most marked at the height of the rash and may persist for several weeks or longer. Occasionally, it is minimal or absent (8, 15, 24).

The rash in rubella is pink and maculopapular

and may be accompanied by fever, coryza, and a mild bulbar conjunctivitis. It appears first on the face and spreads rapidly downward, often within hours. Frequently it fades so quickly that it may be gone from the face by the time it appears on the lower extremities. As it clears from the face, the lesions on the trunk may coalesce; on the extremities, they tend to remain discrete. The eruption may be transitory or it may persist for 4 or 5 days; the average duration is 3 days, thus accounting for the synonym, "3-day measles." Characteristically, there is no residual pigmentation or branny desquamation as in measles; these features have occasionally been observed, however, following rashes of exceptional severity. Histologically, the lesions are characterized primarily by hyperemia and are not distinctive. Attempts to demonstrate rubella virus in these lesions have not been recorded. It is not known, therefore, whether the rash is the result of viral localization or viral multiplication at these sites, or both. The eruption may be preceded or accompanied by an enanthem of red spots on the soft palate (Forchheimer spots), but this is not pathognomonic for the disease. Rubella may also occur without rash (8, 11, 14). Although quantitative data are limited, the incidence of such subclinical infections has been estimated as about 25% (16).

As in many other viral diseases, white blood cell counts range from low to normal. Frequently, the number of atypical lymphocytes is increased. The presence in peripheral blood of both Türk and plasma cells (up to 19%) during the first 9 days of the illness, has been reported as a constant feature of the uncomplicated disease (9). They may persist for 6 weeks or longer. Such cells also occur in various other exanthematous disorders, but to lesser degree.

The period of communicability is generally taken as the prodromal period and at least 4 days thereafter (25). Virus has been regularly demonstrated in pharyngeal secretions for 5 days and in feces for 4 days after onset of rash. It has, however, been sporadically recovered from pharyngeal and rectal swabbings for 14 and 8 days, respectively, after beginning of the eruption and as long as 1 week prior to onset of the rash (8, 16).

Immunity is long lasting and probably lifelong; the extent to which reports of second attacks may represent errors in clinical diagnosis is unknown (2, 11, 26).

Complications in rubella are uncommon. Transitory arthritis, occasionally with effusion (12), encephalitis (22, 23), and purpura (1, 6) have all been observed (11).

γ-Globulin administered after exposure has been recommended for prophylaxis of rubella during the first trimester of pregnancy because of risk to the fetus (17). Its efficacy in preventing this disease, however, has not been clearly established (19). Recent studies indicate that γ-globulin administered to susceptible children within 24 hr after natural exposure to rubella reduces incidence of rash but does not prevent subclinical infection (8, 10). Since γ-globulin may mask rather than prevent the disease, its value for prophylaxis during pregnancy has recently been questioned (16).

A significant reduction in clinical rubella has been recorded among recruits who received γ-globulin prior to exposure (10). This suggests that such attempts at prophylaxis may be useful in certain situations where risk of infection is high (e.g., for susceptible women in early pregnancy whose children have been exposed). It should be noted, however, that the effect of γ-globulin administered prior to exposure on the incidence of inapparent infection is, at present, unknown.

Differential Diagnosis

Typical cases of rubella occurring during an outbreak can generally be recognized without difficulty. That less typical cases may also occur is confirmed by recent viral studies (24). Although rubella virus was recovered from 16 of 20 patients with typical clinical rubella, it was isolated as well from 14 of 21 patients with morbilliform rash but without adenopathy, from 1 of 25 with the diagnosis of scarlet fever, and from 4 of 13 cases with exanthems atypical for rubella. Since the clinical recognition of rubella depends upon the presence of features characteristic of this disease, it is apparent that the diagnosis in atypical cases can be made with certainty only in the laboratory.

A wide range of conditions may be associated with maculopapular eruptions (3, 18, 28). These include viral infections (rubeola; rubella; infection with certain newer viruses, including enteroviruses and others; and infection with the arboviruses dengue, West Nile, and others), probable viral infections (infectious hepatitis, infectious

mononucleosis, roseola, erythema infectiosum, and cat scratch fever), rickettsial infections (typhus, epidemic, endemic, or scrub; and Rocky Mountain Spotted fever), bacterial infections (scarlet fever, meningococcemia, secondary syphilis, and rat bite fevers), and miscellaneous infections (toxoplasmosis, drug eruptions, and toxic erythemas). Of these, the disorders most commonly confused with rubella, are measles, scarlet fever, and roseola, and, less frequently, erythema infectiosum, infectious mononucleosis, and drug eruptions. It has recently become apparent that infections with certain newer viral agents are also important as a cause of rubella-like disease. In the following sections, the differential features of each of these disorders are reviewed.

Measles. Distinguishing features in this disease include Koplik spots, a shorter incubation period, and a more severe, primarily respiratory prodrome. Additional useful signs are the darker color and different course of the measles rash, its tendency to become confluent on the face, and the brownish staining and fine desquamation of the affected skin during convalescence. Both mild measles and cases modified by γ-globulin may closely mimic rubella. In such cases, the epidemiological history may be especially helpful.

Scarlet fever. The rash of scarlet fever may also simulate that of rubella. On the face, however, the rash is replaced by a confluent erythema with circumoral pallor. On the body, it tends to be punctiform or gooseflesh-like with a rough feel to the touch. Typically, it is more concentrated in areas of skin folds and is generally accompanied by a red, sore throat with exudate and by characteristic changes on the tongue. The rash of scarlet fever desquamates in flakes and sheets. Cervical adenopathy and elevated white cell counts with a polymorphonuclear response are common. Generally, group A hemolytic streptococci can be recovered from the nasopharynx.

Roseola. This is a disease of infancy and is rarely observed before 6 months or after 3 years of age. Onset is usually abrupt with high fever and irritability, these persisting for 3 to 5 days. The rash, which resembles that of rubella, appears as the temperature drops to normal. It generally involves the trunk first and may spread to the extremities and face. The adenopathy may resemble that of rubella but is less marked. The illness is distinguished from rubella by its characteristic clinical course and its more limited age range.

Erythema infectiosum. Recognition of this disease depends on the appearance and evolution of the rash. The eruption appears first on the cheeks as a bright red raised area of erythema (slapped-face appearance) which persists for several days. Subsequently, symmetrically distributed maculopapular lesions appear on the extremities and, in lesser concentration, on the trunk. On the arms and thighs, especially, the lesions enlarge, coalesce, and develop a characteristic lacy appearance as their central areas fade. The rash may persist as long as 2 weeks. Duration, however, is variable, with an average of about 4 days. It may reappear after exercise, skin irritation, or various other stimuli.

Infectious mononucleosis. In this disorder, the rash is inconstant and variable but may occasionally resemble that of rubella. In such cases, early differentiation of this disorder from rubella may be difficult since adenopathy and atypical lymphocytes are present in both diseases. The occurrence of membranous tonsillitis and the presence of characteristic laboratory features in infectious mononucleosis are generally sufficient to permit differentiation of these disorders.

Drug sensitivity. This may be manifested by a maculopapular eruption closely resembling that of rubella. In such cases, there is no prodrome or characteristic adenopathy, and the course of the rash may differ from that of rubella. In addition, a history of drug ingestion or exposure can usually be elicited.

NEWER VIRAL AGENTS AND RUBELLIFORM RASH

Infection with certain newer viruses may also be associated with eruptions which closely resemble the rash of rubella. Since specific diagnosis of such infections depends primarily on laboratory procedures which are not generally available, it is probable that illness due to these agents is often mistaken for rubella. The number of newer viruses which have been associated with, or etiologically implicated in, such eruptions is well over 20. These include Coxsackie A2, 4, 5, 9, and 16; Coxsackie B1, 3, 4, and 5; ECHO E1, 2, 3, 4, 5, 6, 7, 9, 11, 14, 16, 18, and 19; reovirus type 2; adenovirus types 2, 3, 4, and 7; and respiratory syncytial virus. The role of these agents in eruptive and other disorders has been the subject of several recent comprehensive reviews (3, 13, 21, 28).

Enteroviruses

Infection with various Cosxackie and ECHO viruses may be manifested by febrile illness with rash, either alone or in conjunction with aseptic meningitis. Such rashes have frequently been observed during outbreaks due to Coxsackie A9 and A16 and ECHO 4, 9, and 16. They have also been noted in sporadic cases or small outbreaks due to 7 additional Coxsackie and 10 additional ECHO virus types, as indicated above (13).

Rashes associated with these infections have commonly been maculopapular, but vesicular, scarlatiniform, and various mixed eruptions have all been reported. In general, these rashes are nonpruritic, do not desquamate, and are variable in extent, distribution, and course. With a few of these agents, papular, vesicular, or ulcerative enanthems have also been observed.

Occasionally, the characteristics of the rash may provide a clue as to the infecting virus type. In disease due to ECHO 9, the exanthem, which is usually maculopapular, frequently involves the face, trunk, and extensor surface of the limbs. On the trunk and extremities it clears rapidly, but on the forehead, cheeks, and chin it may become semiconfluent and violaceous and tends to persist (13, 21). In disease due to ECHO 16, the eruption, which is also rubelliform, does not usually appear until the fever has subsided (28, 21). Rash due to Coxsackie A16 is characterized by a vesicular enanthem and a maculopapular eruption which usually progresses to vesicles and affects primarily the hands and feet (21, 28).

Adenopathy with distribution as in rubella has not been a feature of enteroviral disease. It may, however, occur and has been observed during infection with Coxsackie A9 and B5 and ECHO 2, 4, 9, and 16 (13, 21). Enteroviral rashes are more common in infants and children than in older patients (21). The large number of enteroviruses which have been associated with rash suggests that ability to produce such illness may be a general, though variable, property of these agents.

Reoviruses

These agents, formerly designated as ECHO 10, fall into three distinct antigenic types. Although they have been associated with undifferentiated febrile illness and diarrhea in children, their role in human disease has not been conclusively established. Infection with reovirus type 2 has been described in six children with exanthem; in five of these, the exanthem was maculopapular, and in one it was vesicular. The illnesses, which were of mild to moderate severity, were further characterized by fever, malaise, pharyngitis and, less frequently, by cervical adenopathy. In one patient, described in detail, the rash was first noted on the forehead but rapidly became generalized, persisting for 1 week (20).

Adenoviruses

Several of the 28 currently recognized human adenovirus types have been recovered on one or more occasions from patients with scarlatinal or morbilliform eruptions (7, 21, 28). In one patient, infection with adenovirus type 3 was associated with illness resembling roseola (28). In another, a 3-month-old infant studied in this laboratory, infection with adenovirus type 2 was accompanied by rubelliform rash and adenopathy consistent with rubella. On the other hand, adenovirus types 4 and 7 were recovered in high percentage from throat, feces, urine, and sera of naval recruits with rubelliform illness but were present in similar degree in throat swabbings of a control recruit group without such illness. It is possible in this instance that association of these agents with rash may have reflected a widespread distribution of adenovirus types 4 and 7 among the recruit groups. At present, the relationship of adenoviruses to exanthematous disease is not clear. It is of interest, however, that types 3 and 7 have been repeatedly recovered by different investigators from patients with exanthematous disease (7, 28).

Respiratory Syncytial Virus

This agent has been causally related to croup and other respiratory disorders. Recently, infection with this virus has been associated, in a 2-year-old boy, with febrile exanthematous disease characterized by maculopapular rash (4). Similar infection in a mother and her newborn infant was characterized by a macular and petechial eruption (4).

CONCLUDING REMARKS

It is apparent from this discussion that clinical gradations and atypical cases of rubella may occur. It is evident, as well, that illness with features resembling those of rubella may sometimes be due to other causes. Thus, rubella-like illness may be incorrectly diagnosed as rubella, and atypical rubella, in turn, may be mistaken for various

other disorders. Evidence that erroneous diagnoses are common in this disease is provided by results of a study on 464 pregnant women wherein attempts were made to correlate the patient's history of rubella with presence or absence of antibody (26). No correlation was observed. This suggests that "the occurrence of rubella as reported by patients cannot be taken as a reliable index of previous exposure" (26).

Although various well-defined clinical entities such as measles and scarlet fever may occasionally be mistaken for rubella, such disorders can generally be differentiated on careful evaluation, by their distinctive clinical features. Rubelliform eruptions associated with the newer viral agents, however, are often poorly characterized clinically, and may lack such distinguishing features. That these newer viruses are an important cause of exanthematous disease is apparent from the increasing number of reports relating them to such illness. Infections with these agents are common, beginning early in life, and it is probable that such infections are responsible for certain cases of rubella in individuals who are said to have had multiple episodes of this disease. The extent to which these newer viruses are diagnosed as rubella is unknown.

In summary, it is clear that the clinical diagnosis of rubella may be made with assurance only in typical cases occurring during an epidemic. In sporadic and less typical cases, the diagnosis may be suspected, but it can be established with certainty only in the laboratory.

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